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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/657,472	09/07/2000	Eric S. Lander	2825.1027-0001	1705

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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/657,472	Applicant(s) LANDER ET AL.	
	Examiner Jehanne Souaya	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *1-30 and 47-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group V, claims 31-46, without traverse in paper number 10 is acknowledged. Claims 1-30 and 47-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. An action on the merits of claims 31-46 follows.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. For example, see Figs 1A-2C, and page 9 of specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Indefinite

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 31-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 and 36 are indefinite because the claims fail to include a positive process step relating back to the preamble. The preamble states a method of diagnosing or aiding in the diagnosis of a vascular disease but the final process step is determining the nucleotide present at position 1186 of the thrombospondin 4 gene wherein the presence of a specific nucleotide is indicative of increased or decreased likelihood of vascular disease. Therefore the method is unclear as to whether it is to diagnose [or aid in the diagnosis] or to determine likelihood of disease.

Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 31-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for predicting the likelihood that an individual will have a myocardial infarction or coronary revascularization by determining the identity of the nucleotide at position 1186 of SEQ ID NO 3 wherein the presence of a C at position 1186 is indicative of an increased likelihood of a myocardial infarction or coronary revascularization as compared with an individual having a G at nucleotide 1186 and wherein the presence of a G at nucleotide 1186

is indicative of a decreased likelihood of having a myocardial infarction or coronary revascularization as compared with an individual with a C at nucleotide 1186, does not reasonably provide enablement for a method of diagnosing or aiding in the diagnosis of any vascular disease, or myocardial infarction or coronary revascularization by detecting a C at position 1186 of any thrombospondin 4 gene or SEQ ID NO 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broadly drawn to diagnosing or aiding in the diagnosis of any vascular disease, or more specifically atherosclerosis, coronary heart disease, myocardial infarction, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolisms by detecting a C at position 1186 of any thrombospondin 4 gene or SEQ ID NO 3. The specification, however, only teaches of a study that detected the presence of a C at position 1186 of SEQ ID NO 3 in a group of patients with MI (myocardial infarction) or coronary revascularization. Further, while the study teaches that 148 of 347 patients had the TSP-4 variant (C at position 1186), the specification teaches that the study found that as many as 142 of 422 control subjects also had the variant. Therefore, while the specification teaches that a statistically significant number of patients carried the TSP-4 variant and thus establishes an association between the TSP-4 variant and MI and coronary revascularization, the specification also illustrates that the presence of the variant allele cannot reliably diagnose a patient with any vascular disease, or MI or coronary revascularization because 34% if the control population also

carried the variant allele. With regard to "aiding in the diagnosis", such a term is unclear as the neither the specification nor the claim make clear how detection of the allele "aids in the diagnosis" of any disease. Such a recitation broadly encompasses "diagnosis" (which was discussed above) as well as situations where the presence of the TSP-4 allele along with other factors will allow diagnosis of any vascular disease. Such factors could include other aberrant genes or mutations, which the specification provides no examples of. Such factors could also include risk factors, such as smoking or obesity or diabetes, again, which the specification provides no examples of. The specification provides no teaching or examples of the presence of the TSP-4 allele along with any of these factors leading to a diagnosis of atherosclerosis, coronary heart disease, MI, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

With regard to any thrombospondin 4 gene, the specification only provides an example of an association between MI or coronary revascularization and a C at position 1186 of SEQ ID NO 3. The specification, however, does not teach how the resulting missense mutation in the protein encoded by SEQ ID NO 3 (alanine to proline) is linked to Mi or coronary revascularization, let alone any vascular disease. Such a teaching is critical to enable the broad scope of the invention as TSP-4 genes are present in different species that have less than 100% identity to SEQ ID NO 3. For example, the mouse sequence has 79% identity, the rat sequence has 78% identity, and Xenopus laevis has 44% identity with positions 500-2000 of SEQ ID NO 3 (sequence alignments provided). Without a teaching from the specification or the art as to the significance or role of

amino acid 347 of TSP-4, such as how it interacts with other amino acids within TSP-4 or other proteins involved in the same biochemical mechanism as TSP-4 to achieve wild-type activity, and why or how the presence of a proline instead of an alanine at that position results in an association between MI or coronary revascularization in patients, one of skill in the art would not be able to establish a predictable correlation between the substitution of a C instead of a G at position 1186 of any TSP-4 gene from any species and an association between MI or coronary revascularization, let alone any vascular disease in any individual (encompasses an animal). There specification provides no evidence of a mutation at position 1186 of any other thrombospondin 4 gene, such as a splice variant of SEQ ID NO 4 or TSP-4 from another organism. It is unpredictable whether this position correlates in terms of function with any thrombospondin 4 gene, or whether the exact nucleic acid mutation will result in the same amino acid change. To practice the invention as claimed, the skilled artisan would be required to perform trial and error analysis. Because neither the specification nor the art teach how this position functions in the wild type activity of thrombospondin 4 (SEQ ID NO 3) or how the mutation alters function to provide an association between MI or coronary revascularization, the results of such an analysis are unpredictable and therefore, require undue experimentation.

The claims also broadly encompass diagnosis of or increased risk for any vascular disease based on the presence of a C at position 1186 of any TSP-4 gene or SEQ ID NO 3. The specification, however, does not enable the full scope of the claims. The specification teaches of study that found an association between a C at position 1186 of SEQ ID NO 3 and MI or

coronary revascularization. The specification provides no teaching of the affect of a missense mutation (alanine to proline) at position 347 of SEQ ID NO 4 on the activity of TSP-4 such that the aberrant protein leads to MI or coronary revascularization. Without such teaching, the skilled artisan would be unable to determine how or if the affect of the TSP-4 variant on TSP 4 activity would predictable result in an individual suffering from any vascular disease. Further, the term vascular disease encompasses a large number of disorders that are not all related in terms of biochemical pathways or cause. That is, while a mutation in a gene may be associated with one disease, the mutation may affect the activity in a pathway that is unrelated to other vascular diseases. For example, the On-line Medical Dictionary (cancerweb.ncl.ac.uk/omd/) defines a peripheral vascular disease as a term used to describe progressive occlusive disease of the arteries that supply the extremities and further teaches that risk factors include diabetes. The On-line Medical Dictionary defines a thromboembolism as an obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel and a pulmonary embolism as the lodgment of a blood clot in the lumen of a pulmonary artery, causing a severe dysfunction in respiratory function. Neither the art nor the specification provide any teaching of how the TSP-4 variant affects TSP-4 activity to lead to MI or coronary revascularization and therefore, it is unpredictable as to whether the affect of the TSP-4 variant will also cause peripheral vascular diseases, thromboembolisms or pulmonary embolisms. Additionally, the unpredictability of associating a gene variant with any vascular disease based on the association of the variant with a single vascular disease is illustrated by the post filing date

art of Lange et al (Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 22, pp 418-423, 2002) which teaches that a major limitation of using symptomatic coronary artery disease (CAD) endpoints (such as MI) as a study outcome is substantial disease misclassification (see abstract), and that coronary artery calcification (CAC) which is part of the arteriosclerotic process, is an independent predictor of CAD endpoints. Lange further teaches that atherosclerosis is the major cause of coronary artery disease and is influenced by the complex interplay of numerous environmental and genetic factors (see p. 418, col. 1) and that one half of MI's occur in persons without previous symptoms. Therefore, the art teaches of the unpredictability of associating a gene variant with any vascular disease based on the association of the variant with MI. To practice the invention as broadly as it is claimed, the skilled artisan would have to perform a large study of patients including patients suffering from a substantial number of different vascular diseases and a control population to determine whether the TSP-4 variant taught in the specification is significantly associated with any vascular disease, or more specifically, atherosclerosis, coronary heart disease, thromboembolisms, etc. As the results of such a study are unpredictable due to the lack of guidance from the specification and the unpredictability taught in the art, such experimentation is considered undue.

Conclusion

7. No claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
July 24, 2002